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Triglycerides and Cardiovascular Outcomes—Can We REDUCE-IT?

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Abstract

The causal linkage between triglycerides and coronary artery disease has been controversial. Most of the trials hitherto have shown marginal or no beneficial effects of reduction of triglycerides (with fibrates) on top of low-density lipoprotein (LDL) reduction. But a significant residual cardiovascular risk remains even after use of high dose of statins. Omega-3 fatty acids have been shown to reduce triglyceride levels and some old trials have shown the benefits of fish oils in reducing cardiovascular events. However, barring a few trials most of the large trials of omega-3 fatty acids are negative. Recently, few large trials have been conducted to see the effects of high dose omega-3 fatty acids on cardiovascular outcomes and some of them have shown promising results on top of LDL reduction.

Keywords
- triglycerides
- cardiovascular disease
- omega-3 fatty acids
- statins

Triglyceride (TG) is one of the most controversial parameters in lipidology after high-density lipoprotein-cholesterol (HDL-C). The genesis of controversy is multifactorial starting from its measurement problems to its role in predisposition for atherosclerotic cardiovascular disease (ASCVD) risk, the varied results in epidemiological findings, and nevertheless the discordant results of randomized control trials (RCTs) versus subgroup analysis.

Pitfalls in Laboratory Assessment

There are multitudes of issues in measurement of TG for evaluation of cardiovascular (CV) risk. These include skewed distribution which necessitates categorical definitions or log transformation, increase in variability of TG with increasing levels, inverse association of HDL-C and Apo A1 with TG and whether the assessment should be made in fasting or non-fasting state.[1,2] More importantly, the raised TG levels may be secondary to a host of secondary causes. It may simply be due to insulin resistance, metabolic syndrome, or type 2 diabetes mellitus (DM). Various secondary causes of hypertriglyceridemia (HTG) are enumerated in ►**Table 1**. According to ACC/AHA (American College of Cardiology/American Heart Association) 2018 guidelines moderate HTG is defined as fasting or nonfasting TG levels of 175 to 499 mg/dL (increased very low-density lipoprotein [VLDL]) whereas severe HTG is defined as fasting TG level of >500 mg/dL (increased VLDL and chylomicrons).[3]

Triglycerides and Cardiovascular Disease Risk

The role of TG in the causation of ASCVD has always been controversial. In addition, the association is not as strong as that of low-density lipoprotein-cholesterol (LDL-C). In 1979, it was suggested by Zilversmit that atherogenesis is caused by raised levels of TG and TG rich (remnants) lipoproteins post-food intake.[4] However, independent relationship of raised TG to the risk of future CV events is still questionable. Further, it is a well-known fact that patients of chylomicronemia syndrome do not develop ASCVD and this creates a state of dilemma about TG's relationship to cardiovascular disease (CVD).

Evidence of Role of TG in the Causation of CVD

In 1980, the seminal article published in the *New England Journal of Medicine (NEJM)* concluded that the independent

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Table 1 Various secondary causes of hypertriglyceridemia

Obesity
Insulin resistance
Diabetes mellitus
Hypothyroidism
Gammopathies
Nephrotic syndrome or chronic kidney disease
Chronic liver disease
Lupus
HIV

relationship of TG to CVD is very feeble and still now the controversy remains unresolved.[5]

Epidemiological Studies

A univariate association of TG to CVD has been found in many cohort studies, but this association was lost if LDL-C and HDL-C were taken into account. Thus, the relationship becomes unclear. Many of the large studies have shown a significant association of TG to CVD (►**Table 2**). Some studies suggest that nonfasting TG is a better predictor of CV risk. However, there is a lack of standardization and reference levels which hinders a general implementation.[6] Thus, HTG diagnosis is still made after 12-hour fasting. Nevertheless, there are countries (Denmark) where nonfasting blood samples are still taken to measure TG levels.

The results of Emerging Risk Factors Collaboration study, the largest epidemiological study which assessed over 300,000 individuals from 68 prospective studies, showed a hazard ratio (HR) of 1.37 (confidence interval [CI] 95%: 1.31–1.47) for coronary artery disease (CAD) with increased TG. This association came down to an insignificant HR of 0.99 (CI 95%: 0.94–1.05) after adjustment for HDL-C and non-HDL-C.[12]

Genetic Studies

There are approximately 30 genetic variants which are associated with increase in TG especially if combined with obesity and lifestyle factors. Of these 30 genetic variants six genetic variants are important—low plateau limit (LPL), APOC2, APOA5, LMF1, GP1HBP1, and GPD1A. They can increase TG substantially and are monogenic disorders. An important finding is that persons who have genetically reduced TG have significantly reduced risk of CAD, and in some studies they found a relative risk reduction of 24 and 46% in CVD for APOA5 and LPL, respectively as compared with non-TG reducing alleles.[13–16] So it appears from genetic studies that high levels of TG-rich lipoproteins or remnant cholesterol are causative of CVD and all-cause mortality.

There are several issues regarding the effect of TG lowering on CVD risk. Many of the trials of statins or fibrate monotherapy which studied the role of baseline TG levels with or without HDL-C levels on CVD risk have excluded patients with high TG of >400 mg/dL. So, it is not known whether reducing TG or triglyceride-rich lipoproteins (TGRLP) provide CV benefits. Second, there is no randomized large scale trials of studying direct effects of TG lowering on CVD risk.

Triglycerides and Statin Trials

It is well known from several studies that statin therapy is associated with significant reduction in all CV outcomes irrespective of baseline risk, gender, presence or absence of diabetes and intensive statin therapy further reduces the risk by approximately 15 to 16%.[17–22] However, even after robust reduction of CV events by statins, a significant amount of residual risk still persists as is evident from studies of statin therapy (►**Fig. 1**). These findings implore that additional agents that act on different targets are required to reduce the remaining risk with statins. But the big question that remains is whether lowering of TG will decrease CV risk or not.

Table 2 Triglycerides and cardiovascular risk in various cohort studies

Study	Year	No. of patients	CV risk after adjustment of other risk factors	Reference
Paris prospective study (Fontbonne et al)	1989	7,038	CHD death higher in patients with higher TG level.	7
MELANY study (Tirosh et al)	2007	13,953	HR = 4.05 (95% CI, 2.68–8.61) with top quartile of TG.	8
Sarwar et al	2007	2,62,525	1.72 (95% CI, 1.56–1.90) after correction of intrapatient variation of TG bias.	9
Patel et al	2009	96,224	70% (95% CI, 47–96) greater risk of CHD death, 80% (95% CI, 49–119) higher risk of CHD, and 50% (95% CI, 29–76%) increased risk of stroke with highest quartile of TG.	10
Emerging risk factors collaboration (ERFC)	2009	300,000	HR = 0.99 (95% CI, 0.94–1.05) after adjustment for HDL-C and non-HDL-C.	11

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HDL-C, high-density lipoprotein-cholesterol; HR, hazard ratio; TG, triglyceride.

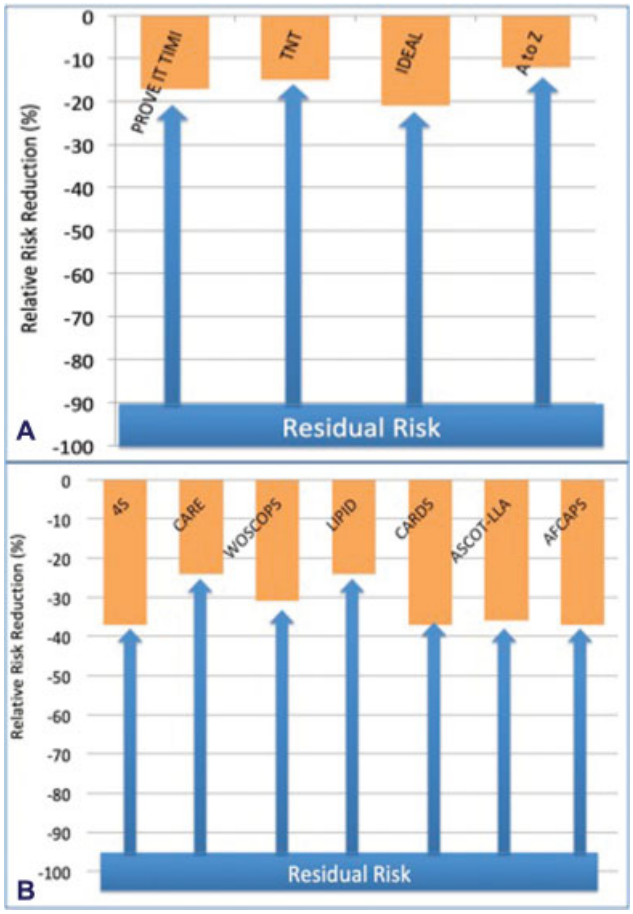

Fig. 1 Residual CV risk after high dose and primary prevention statin trials. The upper panel (**A**) represents secondary prevention trials of statin therapy while the lower panel (**B**) depicts primary prevention studies. AFCAPS, Air Force Coronary Atherosclerosis Prevention Study; ASCOT LLA, the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm; A to Z, Aggrastat-to-Zocor; CARDS—the Collaborative Atorvastatin Diabetes Study; CARE, cholesterol recurrent events; CV, cardiovascular; IDEAL, incremental decrease in clinical end points through aggressive lipid lowering; LIPID, long-term intervention with pravastatin in ischemic disease; PROVE IT, PRavastatin Or Atorvastatin Evaluation and Infection Therapy; 4S, Scandinavian Simvastatin Survival Study; TNT, treating to new targets; WOSCOPS, the West of Scotland Coronary Prevention Study.

Several statin landmark trials and studies have shown increased CV risk with higher baseline TG levels. But only in Scandinavian Simvastatin Survival Study (4S) and Cholesterol Recurrent Event (CARE) trial there was a substantial CV risk reduction in people with higher TG levels. While in the long-term intervention with pravastatin in ischemic disease (LIPID), the Heart Protection Study (HPS), and WOSCOPS (the West of Scotland Coronary Prevention Study), the risk was reduced irrespective of the baseline TG levels. So, it is evident from these studies that statins are beneficial in reducing CV events irrespective of TG levels.[23–31]

Thus, collective data of these studies suggest that patients with high TG are at increased risk for CVD even after statin treatment. However, these patients had additional factors such as metabolic syndrome, raised non-HDL-C, and Apo-B, which might be contributing to additional risk. So, the predictive value of raised TG to CV risk is still uncertain.

Fibrates and Other Nonstatin Drugs for TG Lowering

The trials of TG lowering with fibrates also have conflicting results. The first trial of fibrates was with gemfibrozil for primary prevention in Helsinki Heart Study (HHS) which found significant benefit. The Veterans Affairs HDL Intervention Trial (VA-HIT) with gemfibrozil, which was a secondary prevention trial also had positive results.[32,33] But the subsequent trials with other fibrates were negative. A meta-analysis of 18 fibrate trials comprising of 45,058 patients with or without atherogenic dyslipidemia found a 13% relative risk reduction of any CV event ($p < 0.0001$); however, there was no reduction in stroke, CV mortality, and all-cause mortality.[34] However, another meta-analysis of five studies with atherogenic dyslipidemia ($n = 4,726$) showed 35% relative risk reduction in CV events as compared with only 6% in those with nonatherogenic dyslipidemia (high TG and low LDL-C).[35] Similar trends are seen in a recent meta-analysis of atherogenic dyslipidemia (28% relative risk reduction).[36] As the TG levels were modestly high along with low HDL-C in all these studies, it is not certain whether TG lowering reduced CV risk or not.

The only nonstatin drug with significant CV lowering effect is ezetimibe. There was a 6.4% (95% CI: 1–11%) proportional reduction in major CV events when ezetimibe was combined with simvastatin versus simvastatin monotherapy in the Improved Reduction of Outcomes: Vytorin Efficacy-International Trial (IMPROVE-IT).[37]

So, it is evident that statins are the main drug therapy to reduce CV risk and future CV events. However, a considerable amount of risk still persists after intensive statin therapy. To tackle this several approaches have been tried such as, niacin, cholesteryl ester transfer protein (CETP) inhibitors, fibrates, ezetimibe, omega-3 fatty acids (FA). Among them, there were no benefits of niacin and CETP inhibitors in RCT despite increase in HDL-C and lowering of TG. Lowering of TG with fibrates has shown mixed results. Only ezetimibe showed positive results. While human genetic studies strongly suggest TGRLP to be associated with increased risk of ASCVD, the results of RCTs are not consistent.

Omega-3 FA and TG Lowering—Are There Any Benefits?

The omega-3 FA include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and α-linolenic acid (ALA). These are essential long chain and very long chain polyunsaturated FAs which have got anti-inflammatory properties. EPA, DHA, and DPA are found in fish and other sea foods and other foods supplemented with them, whereas ALA is found in walnuts, leafy vegetables, and oils like canola, soy, and flaxseed oil.

Omega-3 FA are very important for cellular function and influence membrane structure and function, cell signaling, and gene expression. Moreover, they have got various pleotropic effects including reduction of resting heart rate and blood pressure as well as antithrombosis and anti-inflammatory properties[38] (►**Fig. 2**).

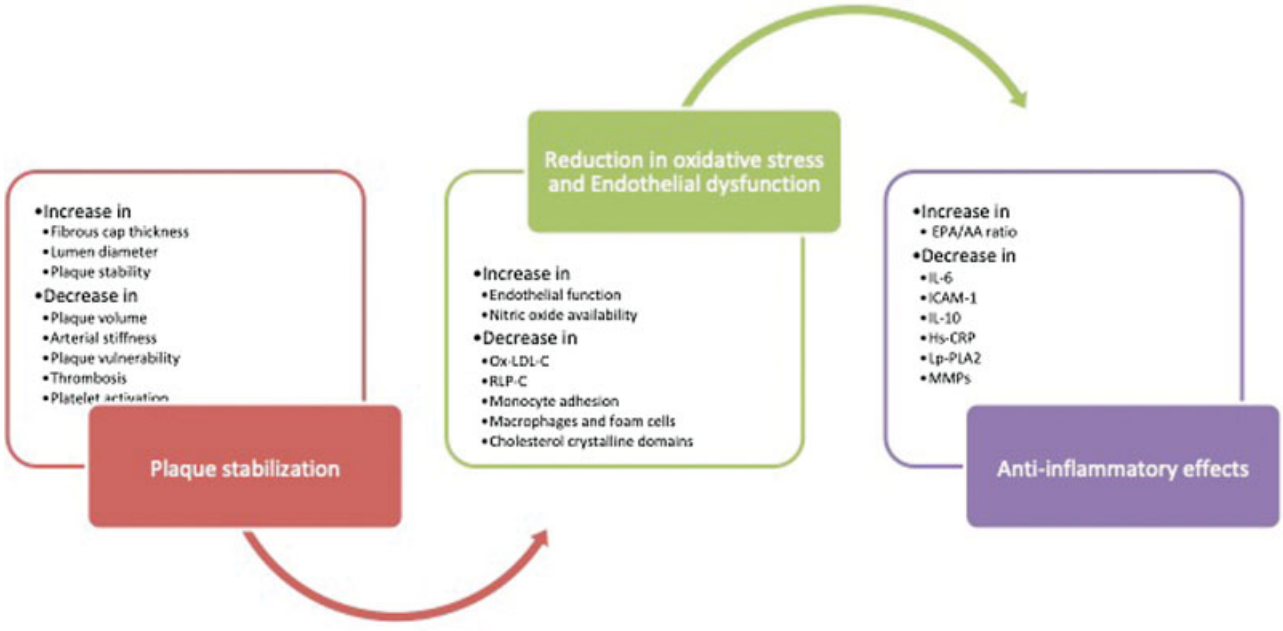

Fig. 2 Potential benefits of omega-3 fatty acids. hs-CRP, high sensitivity C-reactive protein; ICAM-1, intracellular adhesion molecule 1; IL-6, interleukin-6; IL-10, interleukin-10; Lp-LPA2, lipoprotein lipase 2; MMP, matrix metalloproteinases; ox-LDL-C, oxidized low-density lipoprotein cholesterol.

The first observation of beneficial effect of consumption of fish on CV outcomes was made in 1970s in Greenland Eskimo population.[39] These people had relatively less CV mortality. Since then several studies have been conducted on effects of omega-3 FA on CV risk and outcomes.

Early Studies of Omega-3 FA

Early trials which tested the hypothesis of beneficial effects of omega-3 FA found positive results of fish oil on CV mortality.[40,41] This led to the recommendation of omega-3 FA for the primary and secondary prevention of CVD. But further trials did not show any benefits, thus the recommendations for omega-3 FA were later dropped.

The initial Diet and Reinfarction Trial-1 study examined the effect of consumption of fish oil two times or more per week in males who had history of myocardial infarction (MI).[42] They found that there was a significant reduction in fatal coronary heart disease (CHD) events and all-cause mortality but there was no benefit for non-MI recurrence. However, the subsequent Diet and Reinfarction Trial-2 study in males with history of angina showed that consumption of fish oil supplements increased the risk of CV events.[43] Since then several trials of omega-3 FA versus placebo for ASCVD reduction have shown conflicting results.

There have been at least 10 large randomized trials comparing omega-3 FA versus placebo or no treatment with follow-up of 12 months more in patients with prior CHD, stroke, or high risk CVD. These trials have shown conflicting results regarding treatment association for fatal CHD, nonfatal CHD, or other CV diseases. A collaborative meta-analysis of these 10 trials which involved 77,917 patients showed that randomization to omega-3 FA supplementation for a mean duration of 4.4 years did not have any effect on fatal CHD, nonfatal MI, stroke, revascularization events, or any major vascular events.[44] Also there were no significant benefit for major vascular events in any particular subgroups including prior vascular disease, diabetes, lipid levels, or statin intake. These trials used combination of polyunsaturated FA ethyl esters of EPA and DHA except one trial which used EPA alone. The dose of EPA was 226 to 1,800 mg/d while that of DHA was 0 to 1,700 mg/d. Two-thirds of these patients had history of prior CHD, approximately 28% had prior stroke and 37% patients were diabetic. Of these, major vascular events occurred in 15.4% patients which included nonfatal MI (2.9%), death due to fatal CHD, stroke (2.2%), and revascularization procedures (8.5%)[44] (►**Table 3**).

The reasons behind discrepancy of results amongst various studies are unclear. The GruppoItaliano per lo Studio della Sopravvivenzanell' Infarto Miocardico (GISSI) Prevenzione trial was an open label trial which involved 11,323 patients of recent MI.[52] In this trial supplementation with omega-3 FA was associated with 10% reduction in risk of major CV events which was primarily driven by reduction in cardiac death. Whereas, in the Japan EPA Lipid Intervention Study (JELIS) trial which was also an open label trial consisting of 18,645 individuals with total cholesterol >243.24 mg/dL (20% of them had prior CHD), there was a 19% reduction in major CHD events mainly because of reduction in nonfatal CHD.[53] None of the other large placebo-controlled trials showed any benefits.[45,46,54–58] Whether these discrepancies are due to different inclusion criteria for prior disease, different doses of omega-3 FA, or concomitant use of statins is still not known.

Table 3 Old trials of omega-3 FA for cardiovascular risk prevention

Study	Year	Patients (*n*)	Dose of omega-3 FA	Mean trial duration (y)	Mean age (y)	Prior CHD (%)	Prior CVA (%)	Diabetes (%)	Statin use (%)	Reference	End point	RR (95% CI)
GISSI-P	1999	11,334	1 g vs. 300 mg of vitamin E.	3.5	59	100		18.9	137	[45]	Death, nonfatal MI, nonfatal stroke. CVD death, nonfatal MI, nonfatal stroke.	0.84 (0.73–0.97)[a], 0.90(0.81–0.99)[b] 0.80 (0.68–0.94)[a], 0.89 (0.79–0.99)[b]
JELIS	2007	18,645	1.8 g EPA vs. placebo.	4.6	61	20		16.3	100	[46]	Coronary events, fatal and nonfatal MI, unstable angina coronary revascularization.	0.81 (0.69–0.95)
GISSI-HF	2008	6,975		3.9	67	51.8	5.0	28.3		[47]		
SU.FOL.OM3	2010	2,501	600 mg/d EPA + DHA vs. placebo and vitamin B group.	4.2	61	74.5	25.5	17.9	83.1	[48]	Major CV events CHD deaths.	1.08 (0.79–1.47) Not reported
Alpha Omega	2010	4,837	376 mg/d EPA + DHA vs. placebo + ALA (1.9 g/d).	3.4	69	100	7.2	21.0	85.2	[49]	Major CV events CHD deaths.	1.01 (0.87–1.17) 0.95 (0.68–1.32)
OMEGA	2010	3,851	840 mg/d EPA + DHA vs. placebo.	1	64	22.5	5.5	27.0	94.2	[50]	Major CV events Sudden deaths.	1.21 (0.96–1.52) 0.95 (0.56–1.60)
ORIGIN	2012	12,563	840 mg/d EPA + DHA vs. placebo.	6.2	64	64.6	86.8	88.4	53.8	[7]	CVD deaths.	0.98 (0.87–1.10)
R and P	2013	12,513	850 mg/d EPA + DHA vs. placebo.	5	64	30	4.8	59.9	100	[51]	CVD death or CVD hospitalization.	0.98 (0.88–1.08)
AREDS-2	2014	4,203	1 g/d EPA + DHA vs. 10 mg lutein + 2 mg zeaxanthin.	4.5	74	9.7	5	13.0	44.4	[8]	CVD deaths, MI, stroke, unstable angina, coronary or carotid revascularization, hospitalized CHF or resuscitated cardiac arrest.	0.95 (0.780–1.17)

Abbreviations: ALA, α-linolenic acid; AREDS-2, Age-Related Eye Disease Study; CI, confidence interval; CHD, coronary heart disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DOIT, Diet and Omega-3 Intervention Trial; EPA, eicosapentaenoic acid; FA, fatty acids; GISSI-HF, GruppoItaliano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure; GISSI-P, GruppoItaliano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; JELIS, Japan EPA Lipid Intervention Study; MI, myocardial infarction; OMEGA, effect of omega-3 fatty acids on the reduction of sudden cardiac death after myocardial infarction; ORIGIN, outcome reduction with initial glargine intervention; R and P, Risk and Prevention Study; RR, relative risk; SU.FOL.OM3, supplementation en folates et omega-3.

[a]Two-way analysis.

[b]Four-way analysis.

Table 4 Results of latest omega-3 FA trials

Trial	Mean age (y)	No. of patients	Drug used	Mean trial duration (y)	Primary end points	Risk reduction (95% CI)
ASCEND	63.3	15,480	840 mg of omega-3 FA vs. placebo.	7.4	Nonfatal MI or stroke, TIA, or vascular death.	8.9 vs. 9.2% (HR 0.97, 95% CI 0.87–1.08, $p = 0.55$) for serious vascular events) 9.7 vs. 10.2% (HR 0.95, 95% CI 0.86–1.05).
VITAL	67.1	25,871	840 mg of EPA + DHA vs. placebo.	5.3	CV death, MI, or stroke.	3.0 vs. 3.2% (HR 2.2, 95% CI 0.80–1.06, $p = 0.24$) for omega-3 FA 3.1 vs. 3.2% (HR 0.97, 95% CI 0.85–1.1, $p = 0.69$) for vitamin D.
REDUCE-IT	64	8,179	2 g EPA vs. placebo.	4.9	CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina.	17.2 vs. 22% (HR 0.75; 95% CI 0.68–0.83; $p < 0.001$).
STREGNTH		13,086	4 g of EPA + DHA vs. placebo.			Results not out.

Abbreviations: ASCEND, A Study of Cardiovascular Events in Diabetes; CI, confidence interval; CV, cardiovascular; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acids; HR, hazard ratio; MI, myocardial infarction; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; STREGNTH, STatin Residual risk reduction with EpaNova in high CV risk patients with Hypertriglyceridemia; TIA, transient ischemic attack; VITAL, VITamin D and Omega A-3 Trial.

The Post JELIS Era

So to clarify the doubts further large trials were designed like ASCEND (A Study of Cardiovascular Events in Diabetes), VITAL (VITamin D and Omega A-3 trial), STRENGTH (STatin Residual risk reduction with EpaNova in high CV risk patients with hypertriglyceridemia), and REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial)[47–50] (►**Table 4**).

The VITAL trial randomized healthy individual in a 1:1 fashion to either vitamin D3 (dose 2,000 IU/d, $n = 12,927$) or placebo ($n = 12,944$) and either omega-3 FA (1 g/d as a fish oil capsule containing 840 mg of omega-3 FA which contained 460 mg of EPA and 380 mg of DHA, $n = 12,933$) or matching placebo ($n = 12,938$). The mean age of patients was 67.1 years and 61% of the participants were female. Total duration of follow-up was 5.3 years. The primary CV outcome of composite of CV death, MI, or stroke for omega-3 FA versus placebo, was 3.0 versus 3.2% (HR 2.2, 95% CI 0.80–1.06, $p = 0.24$), whereas, for vitamin D3 versus placebo, it was 3.1 versus 3.2% (HR 0.97, 95% CI 0.85–1.1, $p = 0.69$). The all-cause mortality was also not different between omega-3 FA and placebo (3.8 vs. 3.7%). Thus, the supplementation with either vitamin D3 or omega-3 FA was not effective for primary prevention of CV events. But they found that a greater CV benefit was observed in individuals who had lower baseline intake of omega-3 FA.

Also in ASCEND trial there was no benefit of omega-3 FA. In this trial diabetic patients with no other risk factors were randomized in 1:1 fashion to either omega-3 FA (840 mg) or placebo and were followed for around 7.4 years. The composite of major adverse CV events (vascular death, MI, stroke/TIA) occurred in 8.9% of the omega-3 FA group compared with 9.2% of the placebo group ($p = 0.55$).

REDUCE-IT—the Game Changer!

REDUCE-IT is the latest trial of omega-3 FA which has shown positive results. It is a multicenter randomized double-blind placebo controlled trial which involved patients ($n = 8,179$) with established CV risk or having DM with other risk factors. These patients were already receiving statin therapy and had TG levels of 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL. The patients received either 2 g of icosapent ethyl twice a day or placebo and patients were followed for a median of 4.9 years. The primary end point (composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) occurred in 17.2% in icosapent ethyl group as compared with 22.0% in the placebo group (HR 0.75; 95% CI 0.68–0.83; $p < 0.001$) while the secondary end points (composite of CV death, nonfatal MI, or nonfatal stroke) rate was 11.2 versus 14.8, respectively (HR 0.74; 95% CI, 0.65–0.83; $p < 0.001$). There was 25% relative risk reduction in primary end points along with significant reduction in secondary end points on top of statins. Thus, this is a strong evidence in favor of use of omega-3 FA acids in patients with elevated risk for CV events having HTG despite use of statins and well-controlled LDL-C levels (►**Figs. 3** and **4**).

Reduction in Recurrent and Total Ischemic Events by EPA: REDUCE-IT

In this trial, use of EPA was associated with substantial reduction in the burden of first, subsequent, and total ischemic events in patients of established CVD or diabetes with elevated triglycerides on top of statins. There was 30% relative risk reduction in total ischemic events for the primary composite end points (number needed to treat

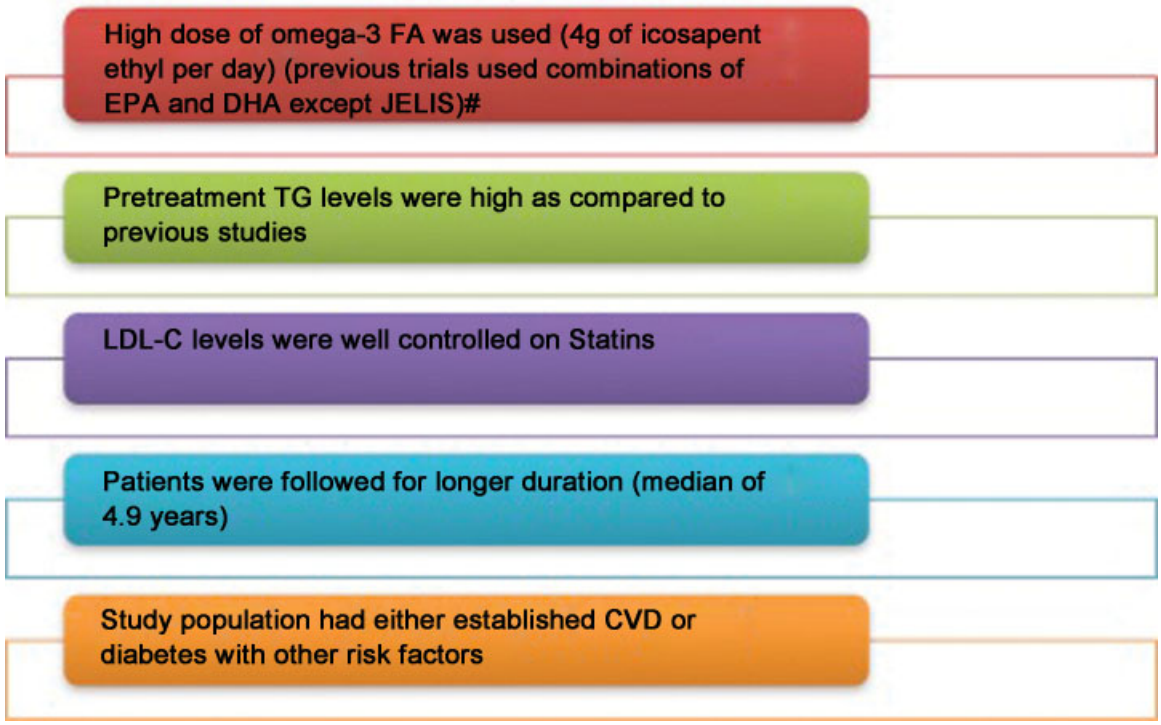

Fig. 3 Salient features of REDUCE-IT. CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; JELIS, Japan EPA Lipid Intervention Study; LDL-C, low-density lipoprotein cholesterol; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.

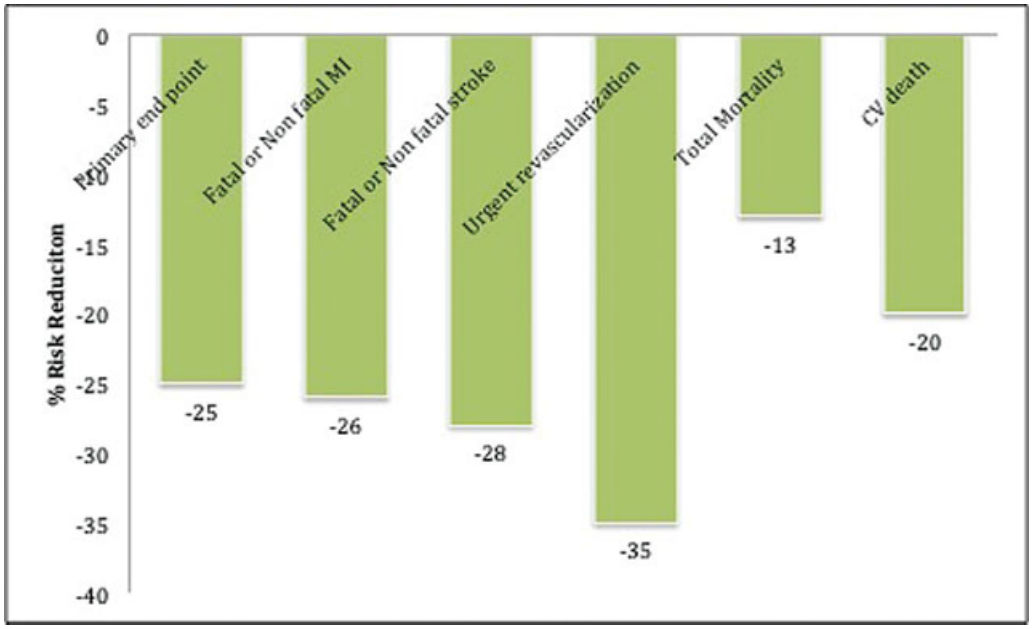

Fig. 4 Reduction in end points in REDUCE-IT. CV, cardiovascular; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.

was 21). The occurrence of first events was reduced by 25%, second by 32%, third by 31%, and fourth or subsequent events by 48%. The secondary ischemic events were reduced by 26% (number needed to treat was 28). Thus in patients with CV risk and HTG, omega-3 FA especially pure EPA can be an important treatment option to further reduce the CV events beyond statin treatment alone.

Guideline Perspective

Although, ignored in previous version, the recently published ACC/AHA cholesterol and prevention guidelines now include persistently elevated high triglycerides (>175 mg/dL) as a risk enhancer for ASCVD risk estimation. In adults with ASCVD risk (estimated by pooled cohort equation) between

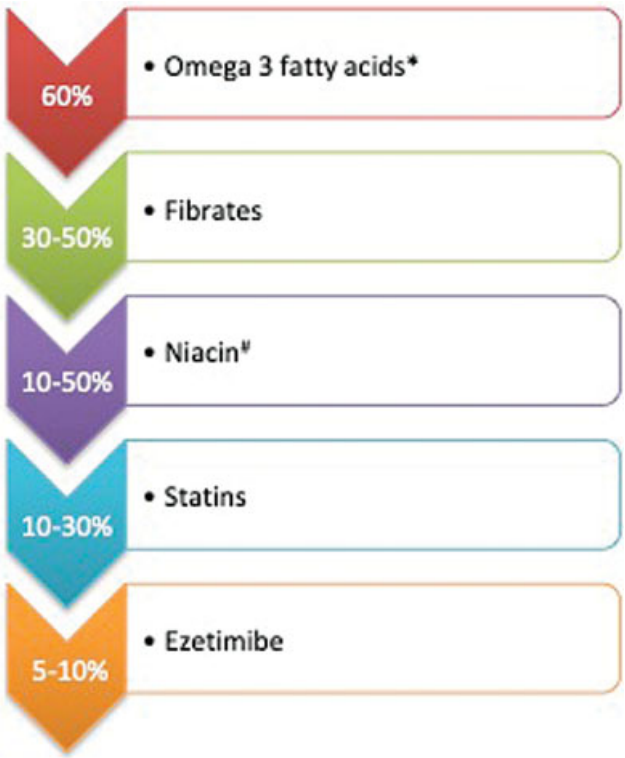

Fig. 5 Triglyceride lowering efficacy of currently available agents. *—In clinical trials, the efficacy varied with baseline TG levels (>500 mg or <500 mg) and dose of omega-3 FA used (Low: 2 g/d, Mid: 3 g/d, High: 4 g/d). #—The TG lowering was higher with immediate release (20–50%) than an extended release preparation (10–30%). FA, fatty acids; TG, triglyceride.

5 and 7.5%, they advocate use of risk enhancers in patient clinician discussion and elevated TGs are now included in the list in lipid biomarkers apart from Apo-B (apolipoprotein B), Lp (a) (lipoprotein a) and Hs-CRP (high sensitivity C-reactive protein).[59,60] A recent scientific advisory from AHA for use of omega-3 FA has suggested use of high dose, that is, 4 g/d pure EPA or combined form of EPA + DHA for treatment of HTG after lifestyle measure and ruling out secondary causes. It can be used as monotherapy or as an adjunct to other lipid lowering drugs. The TG lowering efficacy with currently approved agents is summarized in ►**Fig. 5**.

Conclusion

The association of TG and CV risk has been subject of intense debate and speculation. Although there is robust support from genetic and epidemiological studies, the results of clinical trials TG lowering with fibrates have generally been disappointing. Omega-3 FA supplementation remained a viable target for TG lowering till post JELIS trial. More recently, the exceptional benefits of purified form of omega-3 FA in REDUCE-IT in patients on optimal LDL goals have shifted the focus back on to important issues—the residual risk with statins and benefits of TG lowering with omega-3 FA. Simultaneously, the recent ACC/AHA cholesterol and primary prevention guidelines also recognize high TG as ASCVD risk modulator. Though the results of a few other omega-3 FA trials are awaited, the impressive results of REDUCE-IT will be hard to ignore and it is only a matter of time before either TG and/or omega-3 FA finally find their due space in lipidology.

Conflict of Interest
None.

Acknowledgment of Grant Support
Nil.

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